DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103950/0 (replaces Ref. No. 99-1490)

NOV 14 2001

George Morstyn, Ph.D.
Amgen, Incorporated
One Amgen Center Drive
Thousand Oaks, CA 91320-1789

Dear Dr. Morstyn:

Your biologics license application for Anakinra is approved effective this-date. Amgen, Incorporated, Thousand Oaks, California, is hereby authorized to introduce or deliver for introduction into interstate commerce, Anakinra under Department of Health and Human Services U.S. License No. 1080.

Anakinra is indicated for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs (DMARDs). Anakinra can be used alone or in combination with other DMARDs other than Tumor Necrosis Factor (TNF) blocking agents. Under this authorization, you are approved to manufacture Anakinra at your [redacted] facility in [redacted] 'Final formulated drug product will be filled at your Amgen [redacted] facility in [redacted] In accordance with approved labeling, your product will bear the proprietary name Kineret, and will be marketed in a 100mg/0.67mL dosage strength in 1 mL single-use prefilled glass syringes.

The dating period for Anakinra shall be [redacted] months from the date of manufacture when stored at 2° to 8° C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The bulk drug substance may be stored for up to [redacted] months at [redacted] Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocol in your license application is considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Anakinra to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 2 1 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specification.

Any changes in the manufacturing, testing, packaging or labeling of Anakinra, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 601.27. We are deferring submission of your pediatric studies until December 31, 2004, based on your commitment outlined in item 3 below.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct post-marketing studies as described in your letter of November 13, 2001, as outlined below:

1. To submit data from an ongoing study to evaluate the ability of Anakinra to slow radiographic disease progression. The protocol for study — entitled —

— was submitted to IND — on August 25, 1999. Patient accrual was completed on January 31, 2001, the study will be completed by February 28, 2002, and the final study report will be submitted by July 31, 2002.

2. To submit data from an ongoing study to assess the long-term safety of Anakinra. The protocol for study- ' entitled —

— was submitted to IND — on August 25, 1999. Patient accrual was completed on January 24, 2000, the study will be completed by January 24.2003, an interim report will be submitted by October 1, 2002, and a final study report will be submitted by September 30, 2003.

3. To submit data from an ongoing study to assess the safety and efficacy of Anakinra in pediatric patients with juvenile rheumatoid arthritis (JRA). The protocol for study — , entitled —

—was submitted to IND — on September 17, 1999. Patient accrual will be completed by September 30, 2003, the study will be completed by April 31.2004 and a final study report will be submitted by December 31.2004.

4. To submit data from an ongoing study of the safety and efficacy of Anakinra in combination with Etanercept in patients with rheumatoid arthritis. The protocol for study — entitled —

_____ was submitted to IND ____ on January 9, 2001. Patient accrual will be completed by October 31, 2001, the study completed by April 30.2002, and a final study report will be submitted by December 31.2002.

5. To conduct a multi-center, randomized, controlled study of 250 patients to evaluate the safety and efficacy of the combination of Etanercept and Anakinra, compared to Anakinra alone, in patients with rheumatoid arthritis. This protocol will be submitted by October 31, 2002. Patient accrual will be completed by October 31, 2003, the study completed by April 30, 2004, and a final study report submitted by December 31, 2004.

6. To conduct a multi-center, randomized, controlled study of 500 patients to evaluate the safety and efficacy of Anakinra in combination with Infliximab compared with Infliximab alone in rheumatoid arthritis patients. The protocol for this study will be submitted by January 31, 2002. Patient accrual will be completed by July 31, 2003, the study completed by January 31, 2004, and the final study report will be submitted by December 31, 2004.

7. To conduct an eight-week controlled, randomized study to evaluate the safety and efficacy of vaccination while on Anakinra therapy. The protocol for this study will be submitted by January 31, 2002. Patient accrual will be completed by July 31.2002, the study will be completed by October 31.2002, and a fmal study report will be submitted by June 30, 2003.

8. To submit an analysis of the relationship between adverse events and renal function in patients with rheumatoid arthritis. Differences in the adverse event rates will be compared in one analysis based on creatinine clearance of <30 ml/min, 30 to 50 ml/min, >50 to 80 ml/min and >80 ml/min and in another analysis based on creatinine levels of 1.5 to 2 mg/dL and >2 mg/dL. The analysis of the data will be completed by January 31, 2002, and data submitted by February 28, 2002. Based on the results, if requested by CBER, Amgen will revise the labeling and/or conduct a study to determine appropriate Anakinra doses based on the renal status of patients with rheumatoid arthritis.

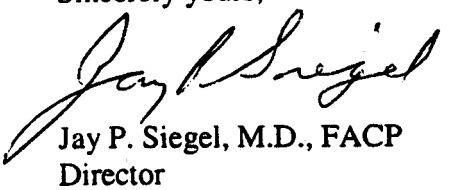
It is requested that adverse experience reports be submitted in accordance with the adverse, experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

'Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a FDA Form

2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,



Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
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